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DATE MAILED: 11/02/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 8/5/93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-9, 11-16 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 10, 17 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-9, 11-16 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

15. Claims 1-9,11-16 are under consideration. Claims 10,17 were cancelled. Claims 1,2,5,7,11-14 were amended.

RESPONSE TO APPLICANT'S ARGUMENTS

16. 35 U.S.C. § 101 reads as follows:
"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

17. Claims 1-9,11-16 remain rejected under 35 U.S.C. § 101 for the reasons discussed in paragraph 16 of the previous Office Action. The rejection of claims 10,17 is withdrawn in view of the cancellation of said claims. Applicant's arguments have been fully considered but they are not deemed persuasive. Applicant has still provided no evidence of the efficacy of the instant invention for the treatment of humans in vivo. Applicant has provided no evidence that the pig model data presented in the specification apriori establishes that the instant invention will work in humans. Applicant has even pointed out potential differences between human and pig skin (eg. that human skin is more vascularized) that would tend to question the validity of the pig model for establishing utility in humans. Furthermore, no data of any kind has been supplied indicating that the instant invention can be used for the treatment of burn patients or cerebral contusions in humans. Waldmann teaches that the therapeutic efficacy of antibody treatment in humans is unpredictable from in vitro or animal data. Waldmann states "Despite this wide ranging interest, the "magic bullet" of antibody therapy that has been the dream of immunotherapists since the time of Paul Ehrlich has proved elusive. Only one monoclonal antibody has been licensed for clinical use. ". Waldmann also states that results from clinical studies in humans using antibody based therapeutics for the treatment of cancer did not fulfill the hopes engendered by in vitro and animal model studies (see page 1660, second column, last paragraph). Waldmann teaches that even human antibodies can be immunogenic by virtue of their idiotypic elements(see page 1659, first column, lines 4 and 5). Harris et al. teach that, "There is widespread acceptance that there is little future for the use of rodent mAbs for in vivo human therapy" and goes on to list problems encountered upon the use of murine antibodies for human therapy (see page 42, second column, first paragraph). These statements confirm what is already known in the art, that the therapeutic efficacy in humans of any particular antibody preparation is sufficiently unpredictable that said efficacy can not be reliably predicted in the absence of human data. No copy of the Montagana et al. reference has been provided,

therefore said reference has not been considered.

18. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

The specification is objected to for the reasons discussed in the previous Office Action in paragraph 17, sections A and B.

19. Claims 1-9,11-16 remain rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification. The rejection of claims 10,17 is withdrawn in view of the cancellation of said claims. Applicant's arguments have been considered and deemed not persuasive. With regards to section A, the claims remain rejected for the reasons elucidated in paragraph 17 of the previous Office Action and paragraph 17 of the instant Office Action. With regards to section B, applicants arguments have not been found persuasive. Applicant has provided no evidence that inhibitors of a natural anticoagulant other than antiprotein c antibodies will reduce microvascular bleeding. The fact that antibodies against protein s will inhibit one function of protein s in a totally unrelated assay does not apriori establish that antiprotein s antibodies will work in the instant invention. No evidence has provided with regards to the other listed compounds and their ability to work in the instant invention.

20. The rejection of claims 1-9,11-16 under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification in paragraph 17, section C of the previous Office Action is withdrawn in view of applicant's arguments. The rejection of claims 10,17 is withdrawn in view of the cancellation of said claims.

21. Claims 1-9,11-16 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited for the reasons detailed in paragraph 19 of the previous Office Action. The rejection of claims 10,17 for the aforementioned reason is withdrawn in view of the cancellation of said claims. The

rejection stands for essentially the same reasons as elaborated in paragraphs 17 and 19 of the instant Office Action.

22. The rejection of claims 1-9,11-16 under 35 U.S.C. § 112, second paragraph is maintained for the following reasons elaborated in paragraph 20 of the previous Office Action. The rejection of claims 10,17 for the aforementioned reason is withdrawn in view of the cancellation of said claims. Claims 1 and 14 are still indefinite in the recitation of "tissue factor inhibitor pathway" because it is unclear what this encompasses. The Broze paper refers to tissue factor pathway inhibitor. Applicant should substitute this phrase for the offending phrase, if this is the compound referred to in the instant claims. Claim 8 is still indefinite for the reason cited in paragraph 20 of the previous Office Action.

23. The rejection of claims 1-4,7,10,15 under 35 U.S.C. § 102(e) as being clearly anticipated by Esmon et al. (US Patent 5,147,638) is withdrawn in view of applicant's arguments and the cancellation of claim 7.

24. The rejection of claims 5,6,8,9,11-13,14,16,17 under 35 U.S.C. § 103 as being unpatentable over Esmon et al. (US Patent 5,147,638) in view of Suzuki et al. is withdrawn in view of applicant's arguments and the cancellation of claim 17.

NEW REJECTIONS

25. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Applicant has not demonstrated the topical use of the instant protein C inhibitor. It is known in the art that effects seen after the systemic administration of a particular agent are not apriori seen when the agent is administered by different routes. Therefore the specification is not enabling for the instant invention.

26. Claim 4 is rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

27. Claims 1-9,11-16 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the use of the HPC-4 antibody in the instant invention. Esmon et al. (US Patent 5,202,253) teaches that this antibody has unique properties which distinguish it from other antiprotein C antibodies, including $CA^{2}+$ dependency (see columns 2). It is not

apparent that any antibody per se against protein C would be able to mediate the microvascular bleeding inhibition effect achieved when this antibody with unique properties is used. In addition it is equally unclear whether non antibody agents that inhibit protein C function would be able to mediate the effect seen using the HPC-4 antibody The enablement is not commensurate with the scope of claims that read on any antiprotein C antibody or protein C inhibiting agent other than the HPC-4 antibody. See M.P.E.P. §§ 706.03(n) and 706.03(z).

28. Claims 1-9,11-16 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the treatment of microvascular bleeding where the HPC-4 antibody is given prior to the initiation of microvascular bleeding as per the experiments depicted in pages 17-21 of the specification. Applicant has provided no evidence as to the efficacy of the instant antibody in treating microvascular bleeding when the antibody is administered after microvascular bleeding has occurred. The enablement is not commensurate with the scope of claims that read on the administration of the HPC-4 antibody after microvascular bleeding has already occurred. See M.P.E.P. §§ 706.03(n) and 706.03(z).

29. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

30. Claims 1-4,7,11-13 rejected under 35 U.S.C. § 103 as being unpatentable over Esmon et al. (US Patent 5,202,253) in view of Esmon et al (US Patent 5,147,638).

The claims are drawn to a method for inhibiting microvascular

bleeding in a patient by blocking protein C function. Esmon et al (US Patent 5,202,253) teaches the antiprotein c antibody of the instant invention(see entire document). Esmon et al. (US Patent 5,202,253) teaches that the antiprotein C antibody can be used to promote clotting (see paragraph four, column 12). Esmon et al. (US Patent 5,202,253) teach that the instant antibody can be used to induce microvascular clotting in a tumor bed (see paragraph three, column 13 and Esmon et al (US Patent 5,147,638)). Esmon et al. (US Patent 5,202,253) teach a pharmaceutical composition of the instant antibody (see paragraph four, column 13). A routineer would have realized that since the antiprotein C antibody can be used to promote clotting, including clotting of the microvascular bed of a tumor, then the instant antibody could be used to promote microvascular clotting in any application that was desired. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have developed a method for inhibiting microvascular bleeding in a patient by blocking protein C function because Esmon et al. (US Patent 5,202,253) teaches the antiprotein c antibody of the instant invention, Esmon et al. (US Patent 5,202,253) teaches that the antiprotein C antibody can be used to promote clotting, Esmon et al. (US Patent 5,202,253) teach that the instant antibody can be used to induce microvascular clotting in a tumor bed and a routineer would have realized that since the antiprotein C antibody can be used to promote clotting, including clotting of the microvascular bed of a tumor, than the instant antibody could be used to promote microvascular clotting in any application that was desired. A routineer would have administered the antiprotein C antibody topically or systemically. Esmon et al. (US Patent 5,202,253) teaches that antibodies against other proteins involved in the mechanism whereby protein C is finally activated can also induce clotting (see column 12, paragraph four). A routineer would have used other inhibitors of protein C in the instant invention in light of the use of antibody against protein C to promote clotting. A routineer would have used the instant invention in any disease where microvascular bleeding was involved such as burns, skin grafts or cerebral contusion. One of ordinary skill in the art would have been motivated to do the aforementioned to treat microvascular bleeding in disease states, in view of the teaching of Esmon et al. (US Patent 5,202,253) that the instant antibody can be used to promote clotting. One of ordinary skill in the art would have a reasonable expectation of success for the aforementioned reasons.

31. Claims 5,6,8,9,14-16 rejected under 35 U.S.C. § 103 as being unpatentable over Esmon et al. (US Patent 5,202,253) in view of Esmon et al (US Patent 5,147,638) as applied to claims 1-4,7,11-13 above, and further in view of Suzuki et al.

The claims are drawn to a method for inhibiting microvascular

bleeding in a patient by blocking protein C function and by also administering a coagulant, and a composition thereof.

Paragraph 26 makes obvious the method for inhibiting microvascular bleeding in a patient by blocking protein C function. Suzuki et al. teach the use of thrombin as a coagulant, when administered systemically or topically for the treatment of injured skin and injured organs (see page 271, first paragraph). It would have been prima facie obvious at the time the invention was made to have developed a method for inhibiting microvascular bleeding in a patient by blocking protein C function and by also administering a coagulant, and a composition thereof because paragraph 26 makes obvious the method for inhibiting microvascular bleeding in a patient by blocking protein C function, and Suzuki et al. teach the use of thrombin as a coagulant, when administered systemically or topically. One of ordinary skill in the art would have been motivated to do so to maximize clotting seen with the instant invention. A routineer would have formulated the instant compounds in a pharmaceutical composition. A routineer would have formulated the appropriate dosage of coagulant. A routineer would have used thrombin or tissue thromboplastin because they are both art recognized coagulants. One of ordinary skill in the art would have a reasonable expectation of success because paragraph 26 makes obvious the method for inhibiting microvascular bleeding in a patient by blocking protein C function, and Suzuki et al. teach the use of thrombin as a coagulant, when administered systemically or topically.

32. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4227.

33. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ron Schwadron whose telephone number is (703) 308-4680. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 180 receptionist whose telephone number is (703) 308-0196.

Ron Schwadron, Ph.D.
October 28, 1993

DAVID L. LACEY
SUPERVISORY PATENT EXAMINER
GROUP 180
10/30/93